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Bacterial lysate treatment in allergic disease: A systematic review and meta-analysis

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Abstract

Objective: The aim of this review was to assess the efficacy of bacterial lysate treatment in patients with allergic disease.

Method: Randomized controlled trials (RCTs) of bacterial lysate therapy for patients with allergic diseases (asthma, atopic dermatitis, and allergic rhinitis) were searched using PubMed, EMBASE, Cochrane, China National Knowledge Infrastructure, Chinese Biomedical literature, and Wanfang databases up to March 2020. Based on the guidelines of the Cochrane collaboration, risk of bias was assessed.

Results: This meta-analysis based on 19 studies comparing bacterial lysate-treated patients with a control group showed a 24% (RR: 1.24, 95% CI [1.19, 1.30]) increase in improvement of allergy symptom control. In addition, the improvement of asthma symptom control was 22% (RR: 1.22, 95% CI [1.14, 1.26]) higher in the bacterial lysate treatment group. Moreover, the levels of immunoglobulin (IgA and IgG), T lymphocyte subtype (CD3+, CD4+, CD4+/CD8+, Th1), and cytokines (IFN-γ, IL-2, and IL-12) were increased in the treated group compared with controls. There was no significant difference in adverse event rate between the two groups.

Conclusion: Treatment with bacterial lysate improves symptom control in patients with allergic diseases on the basis of routine therapy. No adverse risk was found in this meta-analysis.

KEYWORDS
asthma, bacterial lysate, dermatitis, rhinitis, treatment

1 | INTRODUCTION

Currently, allergic diseases have a great impact on the health of children. The childhood incidence rates of asthma, eczema or dermatitis, and allergic rhinitis are increasing gradually, and this increase is even evident in adults.

Atopic dermatitis (AD) is a chronic recurrent inflammatory skin disease characterized by severe itching and eczema-like lesions. It usually occurs in infancy and childhood. A Chinese epidemiology survey in 2014 reported that the prevalence of AD among children from 1 to 7 years old was 12.94% and the trend declined when they are growing up. Its etiology is related to heredity, immunity, and skin barrier function.

According to reports from the World Health Organization, the number of asthma sufferers worldwide has reached 235 million, and as such, asthma represents one of the most common diseases in children. WHO also released the report that the number of deaths caused by asthma was 383,000 in 2015. In 2010, a large-scale

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asthma epidemiology survey of Chinese children aged 0–14 years revealed the overall prevalence of asthma was 3.02% and around one third of children with asthma did not receive a timely diagnosis.[1]

Allergic rhinitis is usually caused by allergens, and the prevalence rate for children may be as high as 40%.[2] Allergic rhinitis and sinusitis are linked to each other, because allergic rhinitis causes the nose to become blocked and in turn blocks the sinuses.[3]

Allergic symptoms vary and differ among individuals and age groups. Some common preventive methods were usually used in allergic diseases such as reduction in exposure to the sensitizing allergen, targeted pharmacotherapy, and some immunotherapies. All of these are very important for the prevention of allergic disease.[4]

Pathogenesis of allergic diseases was proven to involve immune imbalance so that it is believed that some bacterial lysates promote immune responses by increasing immunoglobulin and cellular immunity.[5] Bacterial lysates consist of inactivated bacterial extracts from pathogenic respiratory bacteria. Most of them are divided into two types, either PCBL (polyvalent chemical bacterial lysate) or PMBL (polyvalent mechanical bacterial lysate (PMBL). OM-85 is the most common PCBL used in current studies. It is a lysate of 21 strains of eight bacteria which may boost immunologic responses.[6] Ismigen was the PMBL used in the included studies. This orally/or sublingually administered immunomodulator can activate immunologic defense reactions by increasing IgA and IgG, elevating levels of the Th-1-specific cytokine IFN-γ, and reducing the Th2-specific cytokine IL-4.[7,8]

Some studies have shown that administration of bacterial lysate could reduce episodes in patients with recurrent respiratory infections. According to the result of a double-blind, placebo-controlled, multicenter clinical trial, bacterial lysate treatment could reduce the number of infectious episodes in patients with recurrent respiratory tract infections.[9] The placebo group experienced a mean of 1.43 (95% CI [1.01, 1.86]) episodes in the 8-month study period, while 0.86 (95% CI [0.54, 1.19]) episodes were recorded in the bacterial antigen-treated group. The mean days of antibiotic usage in the treated group was 1.24 compared with 2.83 in the placebo group. Another meta-analysis included 53 studies to assess the efficacy of OM-85 in pediatric patients with recurrent respiratory tract infection found that bacterial lysates could reduce the frequency of respiratory infection.[10]

However, the effect of bacterial antigen treatment on allergic disease remains controversial. Some studies have shown bacterial lysate treatment could reduce asthma attack in terms of duration of coughing and wheezing compared with the control group,[4,11] but others have reported that no significant difference was observed in the number of allergic episodes between treated and placebo groups.[9] For AD, a study by Bodemer and colleagues[12] demonstrated that a 20% reduction in occurrence of repeated events was observed in the OM-85-treated group compared with placebo. Conversely, the result from a randomized placebo-controlled trial including 606 newborns revealed that the prevalence of AD was no difference between the bacterial lysate and placebo groups after 3 years' follow-up. However, it was noted that a significant difference was observed in the group of infants with single heredity for atopy.[13] Feeding bacterial lysate early in life is likely to reduce the occurrence of AD in infants with single atopic family history.

Key Message

Our study showed the effective extent of bacterial lysate therapy on allergic diseases. As three allergic diseases (asthma, allergic rhinitis, and dermatitis) were included in our study, the degree of influence of bacterial lysate on each disease could be assessed. In addition, our research includes not only an evaluation of clinical symptoms but also some serum markers of immunity as well as indicators of lung function.

Therefore, the aim of our study was to investigate the clinical efficiency of bacterial lysate treatment on allergic disease as well as assess the extent of its influence.

2 | METHODS

2.1 | Data sources

We conducted a systematic literature search to identify potential articles from PubMed, EMBASE, Cochrane, China National Knowledge Infrastructure(CNKI), Chinese Biomedical database (CBM), and Wanfang databases. The search was performed using key terms, "broncho-vaxom," "asthma," "dermatitis, atopic," "eczema, atopic," "rhinitis" as well as key words "bacterial lysate," "bacterial extract," "OM-85." All identified articles were imported in Endnote, and selection was based on a three-step procedure, first screening by title, then by abstract, and finally by assessing full texts.

Two reviewers (LCM and CDT) conducted article screening independently, and any disagreements were resolved by discussion.

2.2 | Inclusion and exclusion criteria

In order to be included in this review, studies had to meet all of the following criteria: (1) study design: RCTs without language restriction; (2) participants: children and adults receiving a diagnosis of any type of allergic disease (asthma, dermatitis, allergy rhinitis); (3) intervention group: patients treated with at least one course of bacterial lysate alone, or participants received treatments of bacterial lysate combined with routine allergic disease treatment; (4) comparison group: patients treated with routine therapy for allergic disease or placebo only; and (5) outcome assessment: each study must provide the effective or invalid number. The primary outcome refers to effective/invalid numbers in the bacterial lysate and control groups individually. According to the guide for management and prevention of asthma,[14,15] asthma symptoms could be assessed as

well controlled, partly controlled, or not controlled, by frequency of asthma attack during the day, the efficiency of treatment, activity limitation, or night waking due to asthma. Partly controlled and well controlled were regarded as effective outcomes, and not controlled was defined as an invalid outcome. The effectiveness of treatment on dermatitis and rhinitis was assessed as improvement or no improvement by questionnaire or clinical observation. Secondary outcomes included serum immunoglobulin levels (IgG, IgA, or IgM), or T lymphocyte subtypes (CD3+, CD4+, or CD8+). FEV1 levels or side effects of treatment would be analyzed if mentioned by at least two articles.

Trials were excluded if (1) the study design was not an RCT; (2) no primary outcome number was available; (3) bacterial lysate and other treatments were administered to the experiment group while giving conventional treatment to the control group; and (4) external use of bacterial lysate was applied rather than oral or injected.

2.3 | Statistical analysis

In the meta-analysis of RCTs, dichotomous data were expressed as a relative ratio (RR) with 95% confidence intervals (CI). Continuous data were expressed as mean difference (MD) with 95% CI. Subgroup analysis was performed when at least two studies were concerned. The I^2 statistic was used to assess heterogeneity. When I^2 was between 25% and 50%, it was regarded as low heterogeneity. Moderate heterogeneity and high heterogeneity were reflected by I^2 between 50% and 75%, and 75% and 100%, respectively. When I^2 was below 25%, it was regarded as no heterogeneity. All analyses were performed using StataMP-64. The risk of bias was also assessed by the Cochrane risk bias assessment tool.

3 | RESULTS

3.1 | Study characteristics

A total of 231 references were searched, and after three-step selection, 19 articles[16–34] were finally included, of which 15 studies[16–30] were published in Chinese and four in English[31–34] (Figure 1). One thousand seven hundred and twenty-eight patients were recruited in this study, of which 881 and 841 belonged to the bacterial lysate treatment and control groups, respectively. Out of those 19 articles, 17 studies used OM-85 treatment as intervention therapy. The remaining two studies used polyvalent bacterial lysate (PBL) and killed mycobacterium vaccae as their intervention treatment. Twelve RCTs described results in asthma, four for dermatitis, and three for rhinitis. All 19 studies reported the number of symptom improvement. Five studies and six studies analyzed the level change of T-cell subgroups and interleukins, respectively. Two studies showed the level of serum immunoglobulin and four studies involved the change of FEV1. Only two studies reported the adverse events. Four RCTs included adults, while the remaining 15 studies concerned children (Table 1).

3.2 | Assessing the risk of bias in included studies

Randomization methods were reported in 19 studies. Results of some studies were assessed by questionnaire, whereby the nonblinding of outcome assessment may lead to overestimation of results. In addition, as bacterial lysate usually took at least 3 months to show its effect, some studies with shorter follow-up times may mask the real effect which leads to underestimated results. And, in some studies, the methodology was described in insufficient detail to assess the risk of bias (Figure 2A,B).

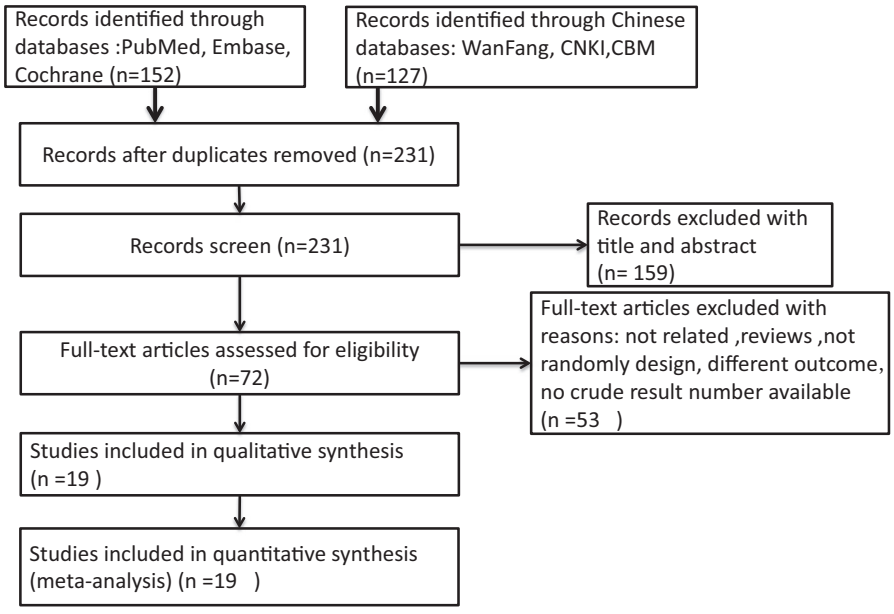

FIGURE 1 The literature search and selection process

TABLE 1 Characteristics of included studies

Study	Publisher year	Type	T/C	Intervention		Followed	Age (year)	Endpoint
				T	C			
Yang Xing	2017	Asthma	44/44	OM-85	Budesonide Aerosol	21 days	T:6.28 + 1.31 C:6.35 + 1.17	1, 2, 3, 5, 6
Cao Jian	2016	Asthma	36/36	OM-85	Terbutaline	10 days	T:35.4 + 8.7 C:39.9 + 10.4	1, 4
Zhang Tian	2018	Asthma	48/47	OM-85	placebo, routine therapies	3 months	T:6.2 ± 0.5 C:5.8 ± 0.7	1, 3
Cheng Yang	2015	Asthma	67/54	OM-85	Pulmicort Respules	21 days	T:5.2 ± 2.2 C:5.4 ± 1.3	1, 2, 3
Yang F	2017	Asthma	43/43	OM-85	Pulmicort Respules	3 weeks	T:5.3 ± 2.06 C:5.02 ± 1.82	1, 2
Jiang Yuan	2012	Dermatitis	20/20	OM-85	Loratadine tablets	3 months	3–12	1
Jiang Yuan	2013	Dermatitis	46/45	OM-85	Ebastine tablets	4 weeks	T:40 ± 3 C:39 ± 3	1, 6
Su Huixia	2017	Asthma	65/65	OM-85	placebo	12 months	T:8.59 ± 1.38 C:8.64 ± 1.40	1, 3
Zhang Hua	2019	Asthma	44/44	OM-85	Pulmicort Respules	1 month	T:6.73 ± 0.82 C:6.45 ± 0.74	1, 5
Tang Yuqi	2017	Asthma	44/43	OM-85	Dipropionate powder inhalation Aerosol	4 months	T:7.8 ± 2 C:7.6 ± 1.9	1, 3, 5
Wu Huanting	2019	Asthma	49/49	OM-85	Pulmicort Respules	3 months	T:7.43 ± 2.62 C:7.31 ± 2.71	1, 3
Cai Jierong	2020	Asthma	37/37	OM-85	Pulmicort Respules	6 months	T:2.13 ± 0.46 C:2.21 ± 0.57	1, 4
Cai Weiwei	2019	Asthma	44/44	OM-85	Laboratoire GlaxoSmithKline	3 months	T:46.52 ± 3.2 C:47.62 ± 4.1	1, 2, 5
Hou Jie	2019	Asthma	45/45	OM-85	Terbutaline	2 weeks	T:7.72 ± 2.16 C:7.13 ± 1.86	1, 2
Xu Huai Yuan	2016	Dermatitis	72/72	OM-85	Ebastine tablets	3 months	T:13–58 C:14–61	1
Chen J	2017	Rhinitis	48/48	OM-85	intranasal saline	3 months	4–12	1
G. Banche	2006	Rhinitis	26/15	PMBL	placebo treatment	3 months	T:7–76 C:5–78	1
Berth-Jones J	2006	Dermatitis	54/49	Killed mycobacterium vaccae	Phosphate-buffered saline	6 months	5–16	1
Zagar S	1988	Rhinitis	29/22	OM-85	placebo treatment	6 months	T:6.52 ± 0.96 C:6.81 ± 0.80	1

Note: Endpoints: 1. Improvement of symptoms; 2. the level of T-cell subgroup; 3. the level of interleukins; 4. the level of serum immunoglobulin; 5. the level of FEV1; 6. adverse event.

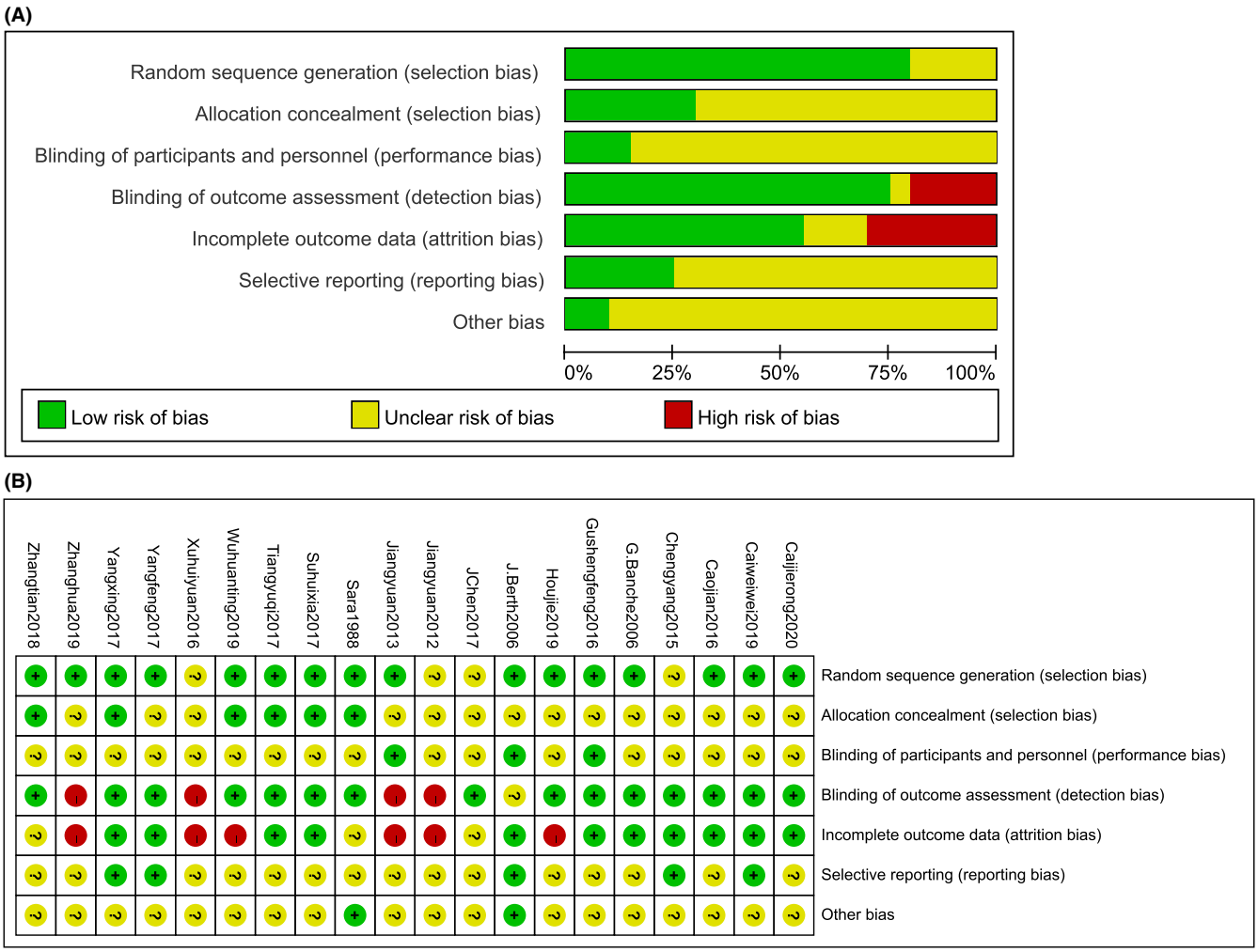

FIGURE 2 (A) The summary of risk of bias. (B) Each risk of bias item for each included study

3.3 | Allergy symptom improvement

A total of 19 RCTs reported improvement of allergic symptoms by assessing symptom control. There were 881 patients in the bacterial lysate-treated group and 847 children in the control group. As shown in Figure 3, allergic symptom improvement was 24% higher in the bacterial lysate group than in the control group. Asthma symptom control (RR: 1.22, 95% CI [1.14, 1.26]) was 22% higher in the bacterial lysate-treated group compared with controls. In addition, the effect size of dermatitis was 1.08 (95% CI 1.0–1.17) which seems to be a small improvement. However, there are only four studies concerned dermatitis treatment. None of the analyses reached statistical significance. Therefore, there was insufficient evidence to conclude that bacterial lysate treatment benefits for dermatitis patients.

On the other side, the total I^2 was 68.7%, which was regarded as moderate heterogeneity. After subgroup analysis by disease type, moderate heterogeneity was found in rhinitis studies. Conversely, lower heterogeneity was observed in asthma and dermatitis studies.

3.4 | Level of T-cell subgroup

After bacterial lysate treatment, the experimental group showed significantly increased CD3+ (SMD = 1.47, 95% CI [1.2, 1.74]), CD4+ (SMD = 1.57, 95% CI [1.33,1.81]), CD4/CD8 (SMD = 0.91, 95% CI [0.67, 1.15]), and Th1 (SMD = 0.48, 95% CI [0.22, 0.74]) cells and significantly decreased CD8+ (SMD = −0.71, 95% CI [−0.95, −0.47]) and Th2 (SMD = −0.61, 95% CI [−0.88, −0.35]) cells (Figure 4).

3.5 | Levels of interleukins

This subgroup analysis showed (Figure 5) that after bacterial lysate treatment, IFN-γ (SMD = 1.0, 95% CI [0.81, 1.19]), IL-2 (SMD = 1.07, 95% CI [0.73, 1.4]), and IL-12 (SMD = 2.4, 95% CI [2.04, 2.76]) were significantly increased, while other factors such as IL-4 (SMD = −0.87, 95% CI [−1.07, −0.68]) and IL-5 (SMD = −2.63, 95% CI [−3.14, −2.13]) were decreased.

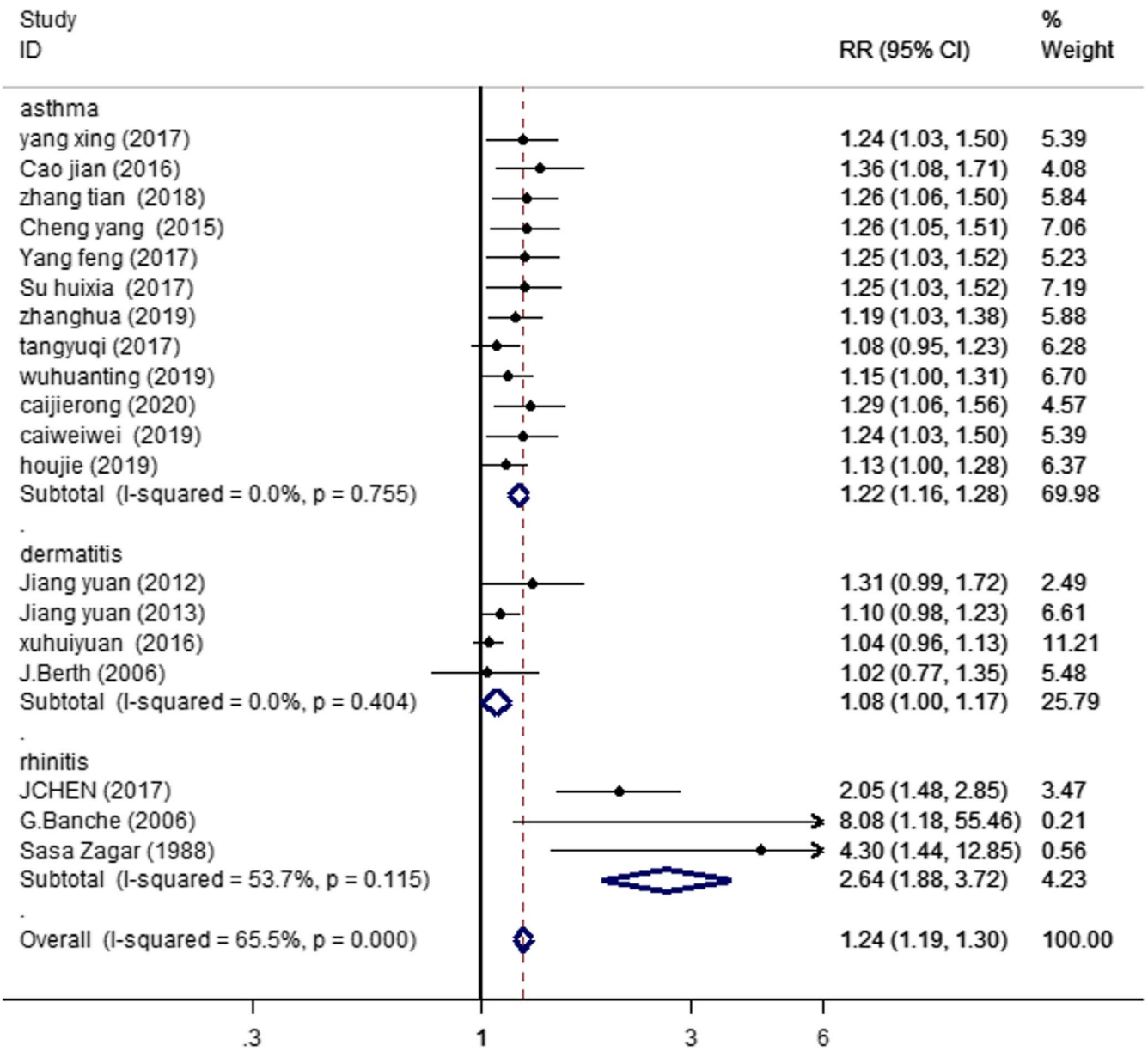

FIGURE 3 The allergy symptom improvement rate in bacterial lysate and control group

3.6 | Level of serum immunoglobulin

The studies regarding IgA and IgM showed high heterogeneity- and all used random-effects models to analyze the data. After bacterial lysate treatment, IgA (SMD = 1.67, 95% CI [1.33, 2.01] and IgG (SMD = 1.00, 95% CI [0.69, 1.31]) were significantly increased, but there were no differences in IgM levels (SMD = 0.05, 95% CI [−0.25, 0.36]) between the two groups (Figure 6).

3.7 | FEV1

The studies regarding FEV1 showed no heterogeneity. The bacterial lysate treatment significantly improved the FEV1 (SMD = 0.53, 95% CI [0.32, 0.74]) (Figure 7).

3.8 | Adverse events

Only two RCTs reported the rate of adverse events. Dizziness, lethargy, nausea, and diarrhea were reported during treatment in both groups, with the results showing that the adverse event rate was not significantly different in the bacterial lysate-treated group compared with controls (RR = 1.27, 95% CI [0.51, 3.09]).

3.9 | Funnel plot of study

From the funnel plot (Figure 8), small-study effect was evident in this study.

There was small-study effect in this study.

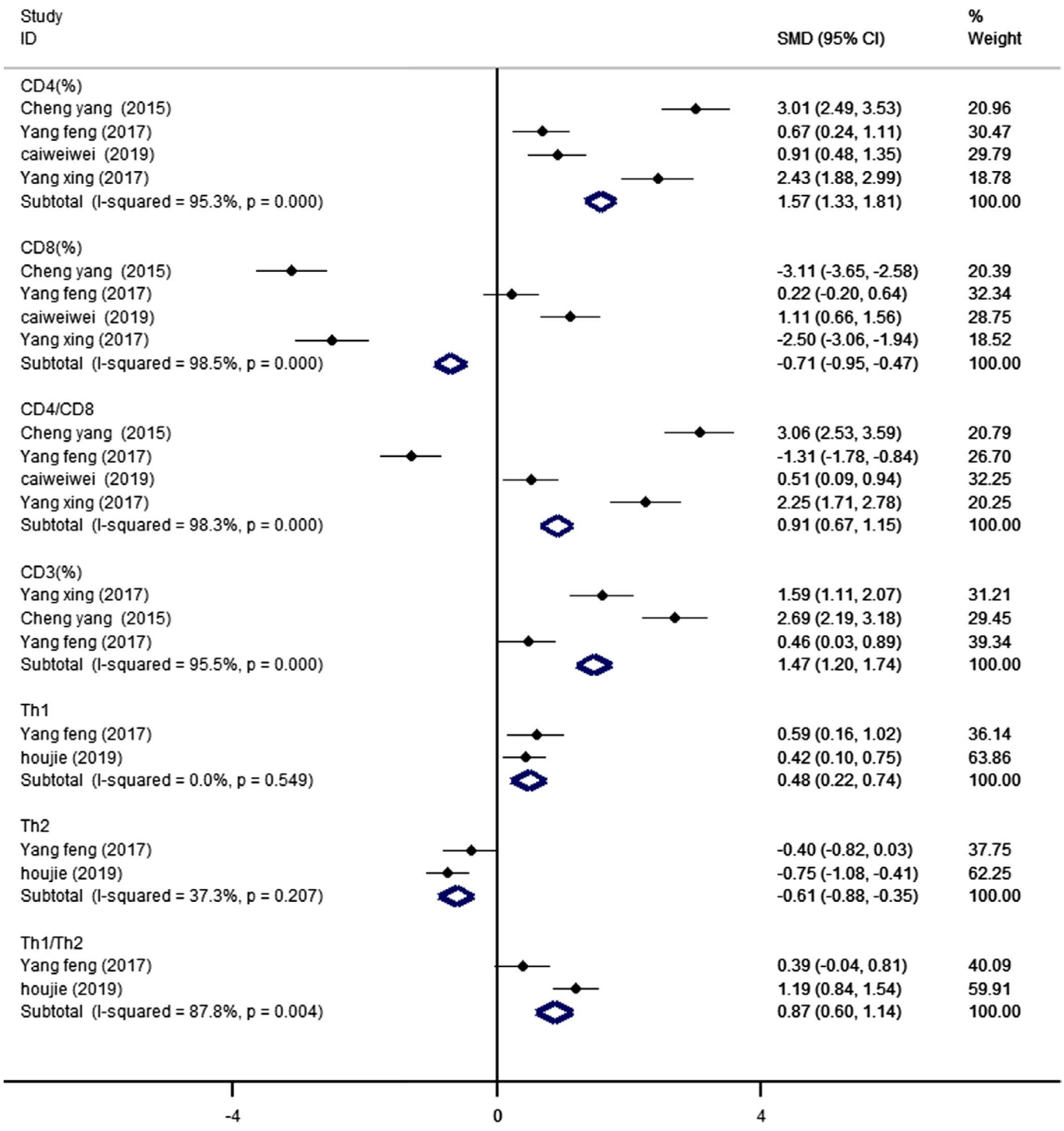

FIGURE 4 The level of T-cell subgroup in bacterial lysate and control group

4 | DISCUSSION

This meta-analysis based on 19 studies comparing bacterial lysate treatment with a control group showed a 24% improvement in allergy symptom control. Additionally, the improvement of asthma symptoms was 22% higher following bacterial lysate treatment, while rhinitis improvement was three times higher in the bacterial lysate-treated group compared with controls. However, there was no difference between bacterial lysate and control groups in dermatitis patients. Moreover, the levels of immunoglobulin (IgA and IgG) were higher in the treated group compared with the control group. Bacterial lysate treatment improved the levels of T lymphocyte subtypes (CD3+, CD4+, CD4+/CD8+, Th1) and decreased CD8+ and Th2 T-cell numbers. Similarly, the bacterial lysate also elevated the levels of IFN-γ, IL-2, and IL-12 while decreasing the levels of IL-4 and IL-5. It was noted that the FEV1 also increased after bacterial lysate treatment, indicating improved lung function.

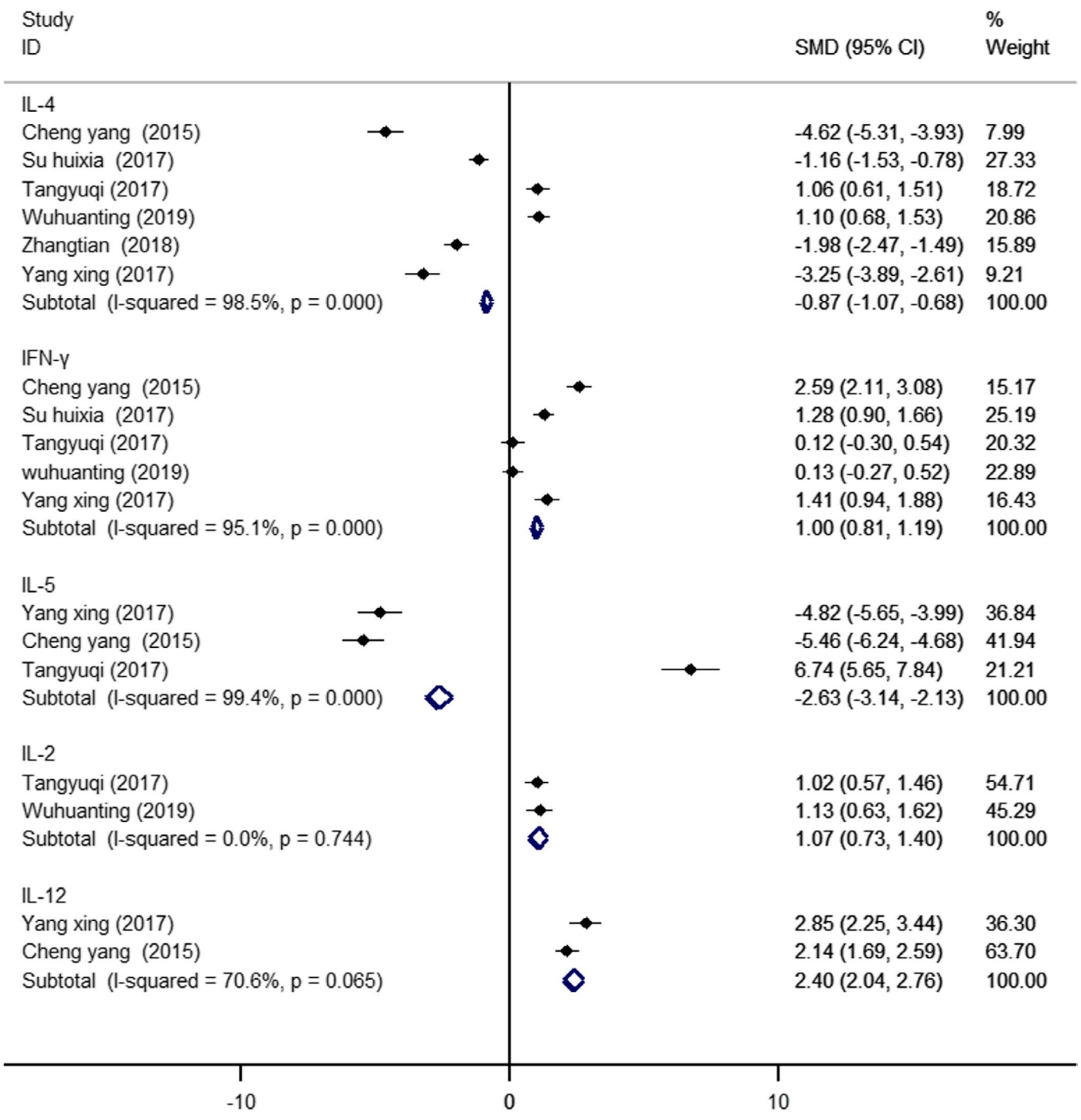

FIGURE 5 The change of IL-4, IFN-γ, IL-5, IL-2, IL-12 in bacterial lysate and control group

Some studies showed the ability of bacterial lysate to prevent respiratory tract infection and asthma exacerbations. One meta-analysis of OM-85 in pediatric recurrent respiratory tract infections showed that OM-85 could not only reduce the frequency of respiratory infections (MD = −2.22, 95% CI [−2.75, −1.90]) but also reduce the duration of wheezing (MD = −3.37 days, 96% CI [−4.52, −2.22]).[13] The trends identified in the present study for IgA, IgG, CD3, and CD4 were similar with this meta-analysis. Another meta-analysis included 5 studies showed the use of bacterial lysate decreased both wheezing episodes (mean difference −2.35 (−3.03–1.67)) and asthma exacerbations (mean difference −0.9 (−1.23–0.57)).[35] The result was similar to our study.

Two further meta-analysis studies investigated the effect of OM-85 on respiratory infection[36,37] and showed that bacterial lysate was beneficial in the prevention of infection in children but presented no data regarding wheezing or allergic disease. Nevertheless, some researches proposed that the decrease in upper respiratory infection may lead to the reduction in asthma exacerbations.

The occurrence of allergic diseases is usually accompanied by an imbalance of the immune system, with skewing away from Th1 and

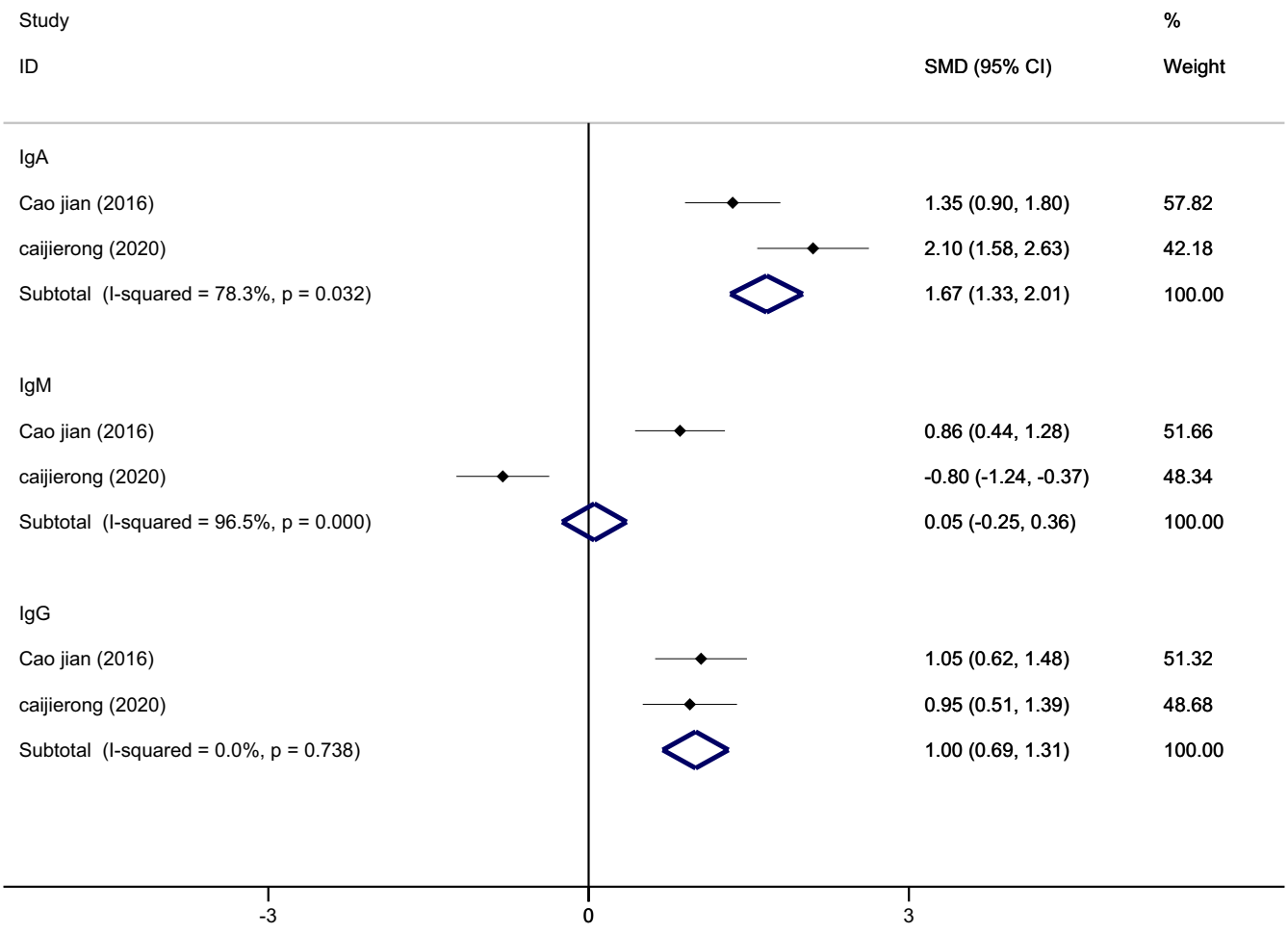

FIGURE 6 The change of IgA, IgM, IgG in bacterial lysate and control group

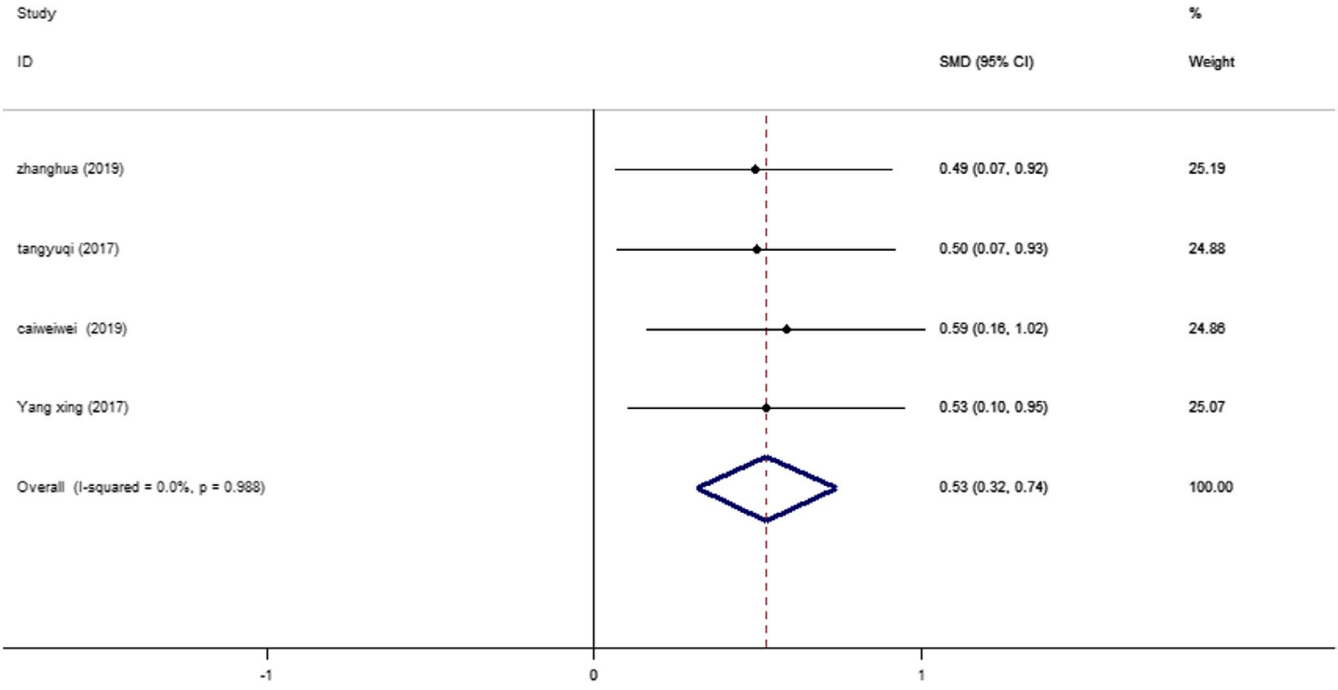

FIGURE 7 The change of FEV1 in bacterial lysate and control group

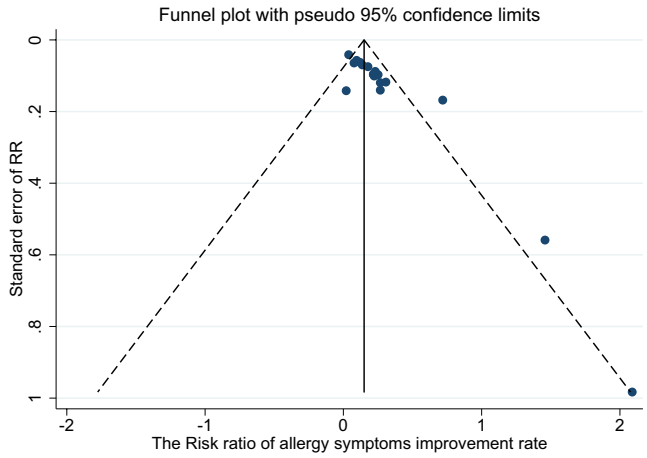

FIGURE 8 Funnel plot of studies

toward Th2. Therefore, many treatments are expected to increase levels of Th1 effectors and reduce Th2 to achieve an immune response that is more Th1-prone. Consistent with this, increased levels of Th1-type cytokines (IFN-γ and IL-2) and decreased levels of Th2-type cytokines (IL-4, IL-5, IL-10) were observed in our study. It could be concluded that bacterial lysate regulates the immune response by altering T-cell subgroups and immune cells. This finding was consistent with other studies[8,38,39] which claimed that OM-85 could induce an immune response shift from Th1/Th2 to Th1. The mechanism by which bacterial lysates stimulate immune responses may concern pathogen recognition receptor ligands containing common motifs shared by pathogenic and commensal bacteria. Furthermore, the changes in gut microbiome diversity following oral administration of bacterial lysates may contribute to immune interactions and influence the immune response.[40–42]

A major strength of our study is the identification of the effective extent of bacterial lysate therapy on allergic diseases. As three allergic diseases (asthma, allergic rhinitis, and dermatitis) were included in our study, the degree of influence of bacterial lysate on each disease could be assessed. In addition, our research includes not only an evaluation of clinical symptoms but also some serum markers of immunity as well as indicators of lung function which can help to evaluate diseases, such as asthma, comprehensively.

However, there remain some limitations related to our study. Firstly, there were 12 RCTs regarding asthma, but only three studies concerned rhinitis and four were related to dermatitis. And the number of studies analyzing some serum indicators was small so that the evidence was not strong enough to draw conclusions. Secondly, due to the extent of unclear and high-risk bias in methodology and study design, the strength of the overall result may be low. Furthermore, the heterogeneity was moderate to high. After subgroup analysis on disease type, moderate heterogeneity was observed in the rhinitis group. The funnel plot of the present study showed asymmetry which means there was a small-study effect. Invalid effective studies are also less frequently published.

5 | CONCLUSION

Our study showed improvement of allergic disease symptoms when bacterial lysate combined with routine treatment was administered. However, because of some high-risk bias and unclear methodologies, these results still require confirmation by high-quality and large sample size studies in the future.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

Chengmei Li: Formal analysis (lead); Methodology (lead); Software (lead); Writing-original draft (lead). **Hua Zhou:** Conceptualization (equal). **Wei Zhang:** Resources (equal). **Datian Che:** Supervision (lead).

ETHICAL APPROVAL

All analyses were based on previously published studies; thus, no ethical approval and patient consent are required.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pai.13572.

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